



A left bundle branch block activation sequence and ventricular pacing influence voltage amplitudes: an in vivo and in silico study

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Abstract: Aims The aim of this study was to investigate the influence of the activation sequence on voltage amplitudes by evaluating regional voltage differences during a left bundle branch block (LBBB) activation sequence vs. a normal synchronous activation sequence and by evaluating pacing-induced voltage differences. Methods and results Twenty-one patients and three computer models without scar were studied. Regional voltage amplitudes were evaluated in nine LBBB patients who underwent endocardial electro-anatomic mapping (EAM). Pacing-induced voltage differences were evaluated in 12 patients who underwent epicardial EAM during intrinsic rhythm and right ventricular (RV) pacing. Three computer models customized for LBBB patients were created. Changes in voltage amplitudes after an LBBB (intrinsic), a normal synchronous, an RV pacing, and a left ventricular pacing activation sequence were assessed in the computer models. Unipolar voltage amplitudes in patients were approximately 4.5 mV (4.4-4.7 mV, 33%) lower in the septum when compared with other segments. A normal synchronous activation sequence in the computer models normalized voltage amplitudes in the septum. Pacing-induced differences were larger in electrograms with higher voltage amplitudes during intrinsic rhythm and furthermore larger and more variable at the epicardium [mean absolute difference: 3.6-6.2 mV, 40-53% of intrinsic value; interquartile range (IQR) differences: 53-63% of intrinsic value] compared to the endocardium (mean absolute difference: 3.3-3.8 mV, 28-30% of intrinsic value; IQR differences: 37-40% of intrinsic value). Conclusion In patients and computer models without scar, lower septal unipolar voltage amplitudes are exclusively associated with an LBBB activation sequence. Pacing substantially affects voltage amplitudes, particularly at the epicardium.

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A left bundle branch block activation sequence and ventricular pacing influence voltage amplitudes: an *in vivo* and *in silico* study

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Aims

The aim of this study was to investigate the influence of the activation sequence on voltage amplitudes by evaluating regional voltage differences during a left bundle branch block (LBBB) activation sequence vs. a normal synchronous activation sequence and by evaluating pacing-induced voltage differences.

Methods and results

Twenty-one patients and three computer models without scar were studied. Regional voltage amplitudes were evaluated in nine LBBB patients who underwent endocardial electro-anatomic mapping (EAM). Pacing-induced voltage differences were evaluated in 12 patients who underwent epicardial EAM during intrinsic rhythm and right ventricular (RV) pacing. Three computer models customized for LBBB patients were created. Changes in voltage amplitudes after an LBBB (intrinsic), a normal synchronous, an RV pacing, and a left ventricular pacing activation sequence were assessed in the computer models. Unipolar voltage amplitudes in patients were approximately 4.5 mV (4.4–4.7 mV, ~33%) lower in the septum when compared with other segments. A normal synchronous activation sequence in the computer models normalized voltage amplitudes in the septum. Pacing-induced differences were larger in electrograms with higher voltage amplitudes during intrinsic rhythm and furthermore larger and more variable at the epicardium [mean absolute difference: 3.6–6.2 mV, 40–53% of intrinsic value; interquartile range (IQR) differences: 53–63% of intrinsic value] compared to the endocardium (mean absolute difference: 3.3–3.8 mV, 28–30% of intrinsic value; IQR differences: 37–40% of intrinsic value).

Conclusion

In patients and computer models without scar, lower septal unipolar voltage amplitudes are exclusively associated with an LBBB activation sequence. Pacing substantially affects voltage amplitudes, particularly at the epicardium.

Keywords

Voltage amplitude • Intra-cardiac electrogram • Heart failure • Left bundle branch block • Activation sequence • Computer models • Anisotropy

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What's new?

- This study investigates the influence of activation sequence on voltage amplitudes in patients and provides possible explanations for these changes using computer modelling.
- In patients and computer models without scar, lower unipolar voltage amplitudes in the septum are exclusively associated with a left bundle branch block activation sequence.
- Ventricular pacing substantially affects voltage amplitudes in both patients and computer models with changes of half the intrinsic value.

Introduction

Low voltage amplitudes from electro-anatomic mapping (EAM) are widely considered as a reference tool for scar delineation¹ and have been associated with scar on delayed enhancement (DE) cardiac magnetic resonance imaging (CMR).² Nevertheless, significant overlap in voltage amplitudes between scar and normal myocardium and substantial inter-patient differences^{3–5} limit the validity of distinct voltage cut-off values to identify scar.⁶

These data suggest that additional factors may affect the voltage amplitudes.⁷ Substantial differences in characterization of scar by low-voltage areas between intrinsic rhythm and ventricular pacing were recently reported,⁸ indicating that the activation sequence influences voltage amplitudes.

Besides during pacing, an abnormal activation sequence can also occur in the presence of inter- and intraventricular conduction disturbances. For instance, a left bundle branch block (LBBB) activation sequence is characterized by a slow impulse conduction originating from the right ventricular (RV) free wall gradually propagating to the left ventricular (LV) free wall.⁹ The influence of an LBBB activation sequence on voltage amplitudes has not been elucidated before.

The aim of this study was to investigate the influence of activation sequence on voltage amplitudes at the endocardium and epicardium in patients with heart failure. In order to improve mechanistic understanding of this influence, regional voltage amplitudes in LBBB patients and computer models without scar were studied. To compare voltage amplitudes during an LBBB activation sequence and a normal synchronous activation sequence, which was not possible in patients, we used highly realistic computer simulations with three customized models of LBBB patients. Additionally, voltage differences induced by ventricular pacing were evaluated both in patients and in computer models.

Methods

Patient population

Patients referred for a cardiac resynchronization therapy (CRT) device implantation who underwent LV endocardial EAM³ or epicardial (coronary venous) EAM¹⁰ were included in this study. To minimize other sources of variation in voltage amplitudes only patients without scar were included. The Comitato Etico del Canton Ticino in Lugano and the Medical Ethics Committee of Maastricht University Medical Center + approved the study protocol.

Electro-anatomic mapping

Patients underwent either endocardial or epicardial EAM. Voltage amplitudes were computed peak-to-peak and activation times were defined as the duration between onsets of QRS-complex on the surface electrocardiogram (ECG) to the moment of steepest downslope on the intra-cardiac electrogram.

Endocardial EAM was performed during intrinsic rhythm using the Noga XP Cardiac Navigation System (Biosense Webster, Irvine, CA, USA) as previously described.¹¹ Unipolar and bipolar electrograms and catheter tip trajectories in three-dimensional space were simultaneously recorded at the entire LV endocardium (bandpass filter: 1–240 Hz). Care was taken to cover the whole LV cavity until the Noga mapped volume was close to the CMR imaging measured volume and the system automatically discards points with insufficient wall contact. All acquired signals were temporally aligned using the simultaneously recorded surface ECG.

Epicardial EAM was performed during intrinsic rhythm and RV pacing using EnSite NavX (Abbott, Chicago, IL, USA) as described previously.¹⁰ A guidewire permitting unipolar sensing and pacing was inserted into the coronary sinus and manipulated to all accessible tributaries, creating an anatomic three-dimensional map of the coronary veins while simultaneously recording electrograms (bandpass filter: 2–300 Hz) and a surface ECG. Right ventricular pacing was performed with the implanted RV lead at 10 b.p.m. above the intrinsic heart rate in DDD-mode with a short atrioventricular (AV) delay to ensure full ventricular capture. Electrograms with poor signal indicating poor contact were manually discarded during the procedure.

Computer models

Three patient-specific computer models were created.¹² Each model geometry was based on CMR imaging of the heart, lungs, and torso surface. The electrophysiological properties of the models were personalized based on the patients' endocardial EAM and 12-lead ECG acquired during sinus rhythm, and geometries were personalized using the CMR imaging-derived heart–lungs–torso anatomies.¹² Simulations were performed with the Propag-5 software¹³ on 2304 cores of the Bullx cluster 'Curie' (TGCC, CEA, France). A ventricular model with a 0.2 mm resolution and a torso model with 1 mm resolution were used. Propagating electrical activity was simulated based on ionic transmembrane currents according to a monodomain reaction-diffusion equation.¹⁴ The Ten Tusscher-Noble-Noble-Panfilov model of the human ventricular cardiomyocyte¹⁵ was used to compute the ionic currents. Computed transmembrane currents were injected at 1 ms intervals in the torso model and the bidomain equation was solved for the electrical potential throughout the torso, from which electrograms at the LV endocardium and epicardium were extracted.¹⁶ A normal activation sequence (synchronous activation) was simulated by inducing multiple breakthroughs in a thin, rapidly conducting endocardial layer mimicking the Purkinje network activation. A RV pacing simulation was created by single-point pacing in the RV endocardium apex, whereas a LV pacing simulation was created by single-point pacing in the LV epicardium. Similar to clinical data, unipolar voltage amplitudes were computed peak-to-peak and activation times were quantified as the duration between onset of the QRS-complex and the moment of steepest downslope on the intra-cardiac electrogram.

Data analyses

Data were expressed as mean \pm standard deviation or median and inter-quartile range (IQR). Analyses were performed in MATLAB 2016b (Mathworks, Natick, MA, USA). Non-parametric test approaches were used for patient data analyses. Statistical significance was not evaluated in the simulated data, as it has been argued that statistical comparisons of computer models are inappropriate.¹⁷ Absolute values were therefore used to describe the simulated data instead. Regional voltage differences

Table 1 Patient characteristics

Patient	Age (years)	Sex	BMI (m ² /kg)	LVEF (%)	Type	NYHA class	Conduction	QRSd (ms)	Wavefronts	Mapping	Number of EGMs
p1	73	F	30	39	NCMP	3	LBBB	139	Intrinsic	LV endo	167
p2	70	M	23	35	ICMP	2	LBBB	179	Intrinsic	LV endo	88
p3	54	M	32	34	ICMP	2	LBBB	165	Intrinsic	LV endo	131
p4	70	M	24	21	NCMP	2	LBBB	160	Intrinsic	LV endo	206
p5	69	F	30	17	ICMP	3	LBBB	185	Intrinsic	LV endo	199
p6	69	F	31	35	ICMP	3	LBBB	156	Intrinsic	LV endo	236
p7	69	M	26	45	NCMP	2	LBBB	154	Intrinsic	LV endo	163
p8	85	M	31	32	NCMP	3	LBBB	180	Intrinsic	LV endo	244
p9	69	M	24	28	ICMP	2	LBBB	170	Intrinsic	LV endo	159
p10	75	M	27	34	NCMP	2	LBBB	142	Intrinsic/RV	LV epi (veins)	50
p11	80	M	26	29	ICMP	2	IVCD	136	Intrinsic/RV	LV epi (veins)	26
p12	42	F	31	28	NCMP	2	LBBB	160	Intrinsic/RV	LV epi (veins)	27
p13	75	F	23	15	NCMP	3	LBBB	122	Intrinsic/RV	LV epi (veins)	47
p14	71	F	26	29	NCMP	2	LBBB	156	Intrinsic/RV	LV epi (veins)	41
p15	65	F	27	10	NCMP	3	LBBB	150	Intrinsic/RV	LV epi (veins)	41
p16	52	M	34	24	NCMP	3	LBBB	136	Intrinsic/RV	LV epi (veins)	19
p17	57	F	25	26	NCMP	2	IVCD	158	Intrinsic/RV	LV epi (veins)	34
p18	60	F	26	20	NCMP	2	LBBB	132	Intrinsic/RV	LV epi (veins)	42
p19	61	M	21	32	NCMP	2	LBBB	154	Intrinsic/RV	LV epi (veins)	48
p20	58	M	28	26	NCMP	3	LBBB	150	Intrinsic/RV	LV epi (veins)	13
p21	80	M	25	24	NCMP	3	LBBB	156	Intrinsic/RV	LV epi (veins)	29

BMI, body-mass-index; EGMs, electrograms; F, female; ICMP, ischaemic cardiomyopathy; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LV, left ventricle; LVEF, LV ejection fraction; M, male; NCMP, non-ischaemic cardiomyopathy; NYHA, New York Heart Association functional; QRSd, QRS duration; RV, right ventricle.

in patients and computer models were compared by subdividing the LV into four segments: anterior, lateral, inferior, and septal. Intrinsic voltage amplitudes were compared between segments and for all patients with endocardial EAM using Kruskal–Wallis tests.

Pacing-induced voltage changes were evaluated in patients with epicardial EAM and in computer models by assessing differences as absolute and relative (percentage of intrinsic value) numbers. For the epicardial EAM patient data, paired comparisons were carried out by matching every electrogram during intrinsic rhythm with the nearest electrogram obtained during RV pacing under the condition that the Euclidean distance between the two electrograms was <15 mm. In the computer models, paired comparisons were performed by comparing electrograms during different activation sequences from the same vertex in three-dimensional space. Relative differences between every paired electrogram (depicted in mV or percentage of intrinsic value) were computed as:

$$\text{Difference [mV]} = \text{intrinsic} - \text{paced}$$

$$\text{Difference [\% intrinsic]} = \frac{\text{intrinsic} - \text{paced}}{\text{intrinsic}} \times 100\%$$

Absolute differences were computed similarly as:

$$\text{Difference [mV]} = \text{abs}(\text{intrinsic} - \text{paced})$$

$$\text{Absolute difference [\% intrinsic]} = \frac{\text{abs}(\text{intrinsic} - \text{paced})}{\text{intrinsic}} \times 100\%$$

Bland–Altman analyses were carried out to evaluate the agreement between voltage amplitudes during intrinsic rhythm and pacing.

Results

Study population

A total of 21 patients and three computer models were included in the study. Nine patients, all with LBBB, underwent endocardial EAM (p1–p9) during intrinsic rhythm, while 12 patients underwent epicardial EAM (p10–p21) during both intrinsic rhythm and RV pacing. Three computer models (s1, s2, and s3) were created based on patient-specific geometries obtained from patients p1, p2, and p3. Detailed information on individual patients and computer simulations is provided in Tables 1 and 2, respectively.

Regional voltage differences in patients with left bundle branch block

Regional unipolar and bipolar voltage differences were evaluated for the nine patients who underwent endocardial EAM during intrinsic rhythm, as these patients had a large number of mapped points covering all segments of the LV.

Mean unipolar voltage amplitudes were approximately 4.5 mV (varying between 4.4 and 4.7 mV, ~33%) smaller in the septum compared with anterior, lateral, and inferior within each endocardially

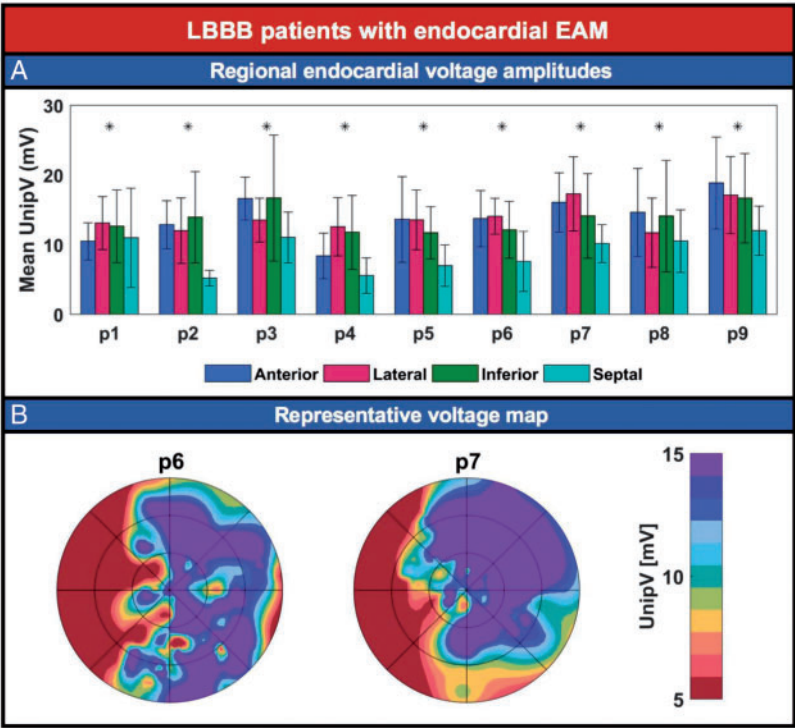


Figure 1 Regional differences on endocardial unipolar voltage amplitudes (UnipVs) in patients with LBBB. (A) Mean \pm SD of endocardial UnipVs per patient grouped according to location. Lower UnipVs are consistently present in the septum. $*P \leq 0.001$ based on Kruskal–Wallis test. (B) Endocardial voltage maps of two representative patients with LBBB. EAM, electro-anatomic mapping; LBBB, left bundle branch block; SD, standard deviation.

mapped patient and for all nine patients together (anterior: 13.5 ± 5.6 , lateral: 13.8 ± 4.8 , inferior: 13.5 ± 6.1 , and septum: 9.1 ± 4.5 mV, $P < 0.001$). Regional unipolar voltage distributions in individual patients and representative voltage maps are provided in Figure 1. In contrast, bipolar voltage amplitudes were more heterogeneously distributed among the LV segments (anterior: 4.8 ± 3.6 , lateral: 5.0 ± 3.1 , inferior: 5.5 ± 3.8 , and septum: 4.7 ± 4.5 mV, $P < 0.001$).

Regional voltage differences in simulations with left bundle branch block and normal activation

Regional endocardial unipolar voltage differences were additionally assessed in three computer models. In all computer models, unipolar voltage amplitudes during an LBBB activation sequence were on average 4.0 mV (~24%) smaller in the septum and inferior compared to other LV segments (anterior: 16.7 ± 3.8 , lateral: 17.3 ± 3.2 , inferior: 13.1 ± 3.7 , and septum: 13.1 ± 4 mV). After inducing a normal synchronous activation sequence in the three computer models, regional unipolar voltage distributions became more uniform (Figure 2), and unipolar voltage amplitudes were on average similar between the segments (anterior: 14.1 ± 3.4 , lateral: 14.4 ± 3.9 , inferior: 13.7 ± 4.4 , and septal: 13.2 ± 4.1 mV).

Right ventricular pacing-induced voltage differences in patients

An overview of pacing-induced voltage changes for patients and computer models is provided in Figure 3. Pacing-induced unipolar voltage changes were analysed in the 12 patients who underwent epicardial EAM (Figure 4). Overall, unipolar voltage during RV pacing did not differ significantly from the value during intrinsic conduction (intrinsic: 7.8 ± 5.0 , RV paced: 8.0 ± 6.9 mV, $P = 0.709$), but RV pacing caused considerable changes in these voltage amplitudes (IQR: 53% of intrinsic value; Figure 3). The absolute change in unipolar voltage amplitude between intrinsic rhythm and RV pacing was substantial: 3.6 ± 5.9 mV ($52 \pm 110\%$ of intrinsic value). Larger unipolar voltage changes were present in electrograms with a larger amplitude during intrinsic rhythm (Bland–Altman analysis in Figure 4C).

Right ventricular and left ventricular pacing-induced voltage differences in computer models

Pacing-induced unipolar voltage differences (Figure 3) at the epicardium and endocardium were additionally evaluated in computer models (Figures 5 and 6, respectively). Similar to the patient data, the direction of pacing-induced unipolar voltage changes could be either positive or negative and larger differences were present in

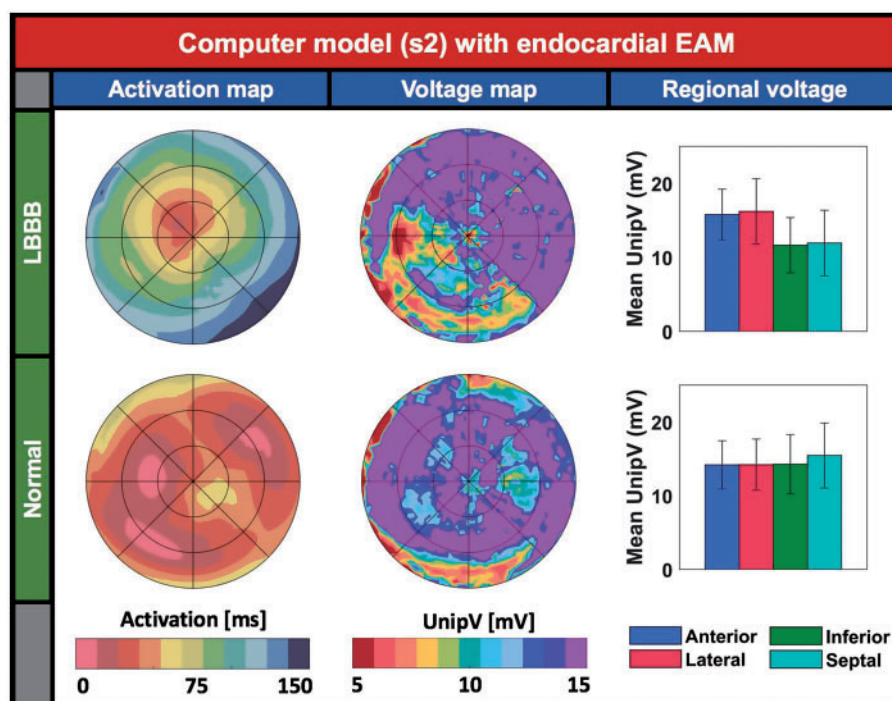


Figure 2 Regional differences in endocardial unipolar voltage amplitudes (UnipVs) in a computer model. Activation (left) and voltage (middle) maps with accompanying location bar graphs (right) of simulations s2 during an LBBB (top panels) and normal (bottom panels) activation sequence. UnipVs are smaller in the septum and inferior during LBBB. These lower voltage amplitudes disappear when a normal activation sequence is restored. EAM, electro-anatomic mapping; LBBB, left bundle branch block.

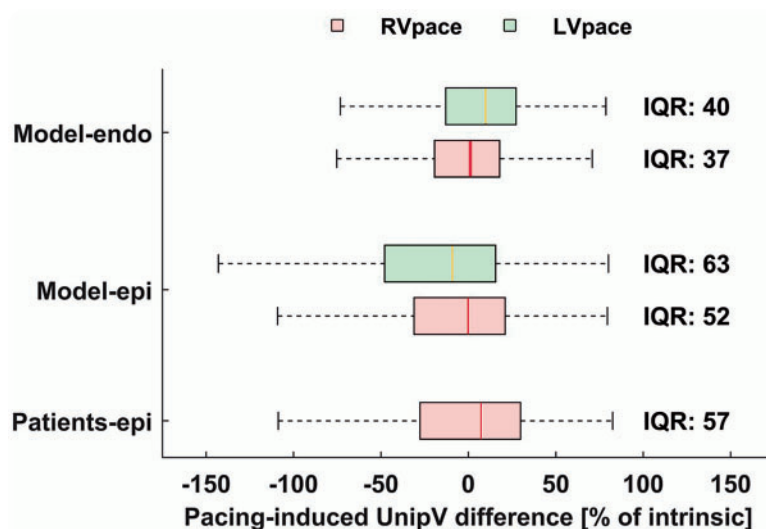


Figure 3 Overview of differences in unipolar voltage amplitudes (UnipVs) values after changing the sequence of activation by pacing. Differences are depicted in percentage of intrinsic value. The red boxplots indicate the differences induced by RV pacing, while the green boxplots indicate the LV pacing-induced changes. The central mark in the box indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers. Changes are grouped for epicardial EAM patients ($n = 9$) and computer simulations ($n = 3$) with both endocardial and epicardial EAM points. The IQR of RV pacing-induced changes of patients with epicardial EAM is very similar to the changes observed at the epicardium in the computer models. The IQR of UnipV changes is generally larger for the epicardium compared with the endocardium and higher after LV pacing compared with RV pacing. EAM, electro-anatomic mapping; IQR, interquartile range; LV, left ventricular; RV, right ventricular.

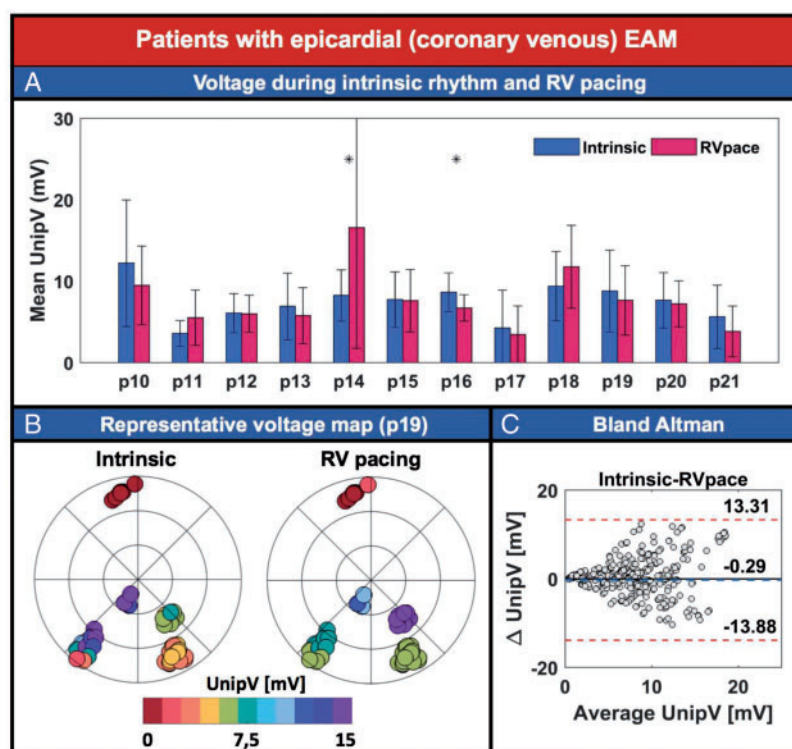


Figure 4 Pacing-induced unipolar voltage amplitudes (UnipVs) changes at the epicardium in patients. (A) Mean \pm SD of endocardial UnipVs per patient during intrinsic rhythm and RV pacing. * $P \leq 0.05$ based on Mann–Whitney U test. (B) Epicardial (coronary venous) UnipV map of a representative patient (p19) during intrinsic rhythm and RV pacing. The mean UnipV does not change much, but substantial changes per electrogram are present. (C) Bland–Altman analyses for UnipV differences between intrinsic rhythm and RV pacing. Right ventricular pacing induces substantial changes in UnipV, although the direction of change varies. The larger the UnipV during intrinsic rhythm, the larger the change after pacing. EAM, electro-anatomic mapping; RV, right ventricular; SD, standard deviation.

electrograms with larger voltage amplitudes during intrinsic rhythm (Bland–Altman analyses in Figures 5C and 6C). Overall there was a positive correlation between the mean- and absolute unipolar voltage differences (from the Bland–Altman plots in Figures 5C and 6C) for both endocardial and epicardial unipolar voltage amplitudes (R 0.1477–0.3881, $P < 0.001$).

Mean epicardial unipolar voltage was distinct for different activation sequences (intrinsic: 17.4 ± 5.9 , RV pacing: 18.7 ± 8.3 , and LV pacing: 19.6 ± 6.4 mV; Figure 5A), with the greatest change in unipolar voltage difference occurring during LV pacing (IQR: 63 and 40% of intrinsic value for epicardium and endocardium, respectively; Figure 3). The absolute mean difference between intrinsic epicardial unipolar voltage and pacing was 6.0 ± 5.9 (40 \pm 53% of intrinsic value) for RV pacing and 6.2 ± 5.3 mV (45 \pm 56% of intrinsic value) for LV pacing.

Mean endocardial unipolar voltage amplitudes were also affected by changing activation sequence (intrinsic: 13.7 ± 4.3 , RV pacing: 14.0 ± 4.7 , and LV pacing: 12.7 ± 4.7 mV; Figure 6A), although these differences were much smaller than the epicardial values (Figure 3). The mean absolute difference between intrinsic endocardial unipolar voltage and pacing was 3.3 ± 3.2 (28 \pm 33% of intrinsic value) for RV pacing and 3.8 ± 3.2 mV (30 \pm 30% of intrinsic value) for LV pacing.

Discussion

This is the first study elucidating the voltage distribution during an LBBB activation sequence and investigating pacing-induced voltage changes in patients with possible explanations provided by computer simulations. We demonstrated that an LBBB activation sequence, in the absence of scar, is associated with lower unipolar voltage amplitudes in the septum. We furthermore showed, using computer modelling, that these LBBB-associated low septal unipolar voltage amplitudes are functional, because they are completely abolished during a normal synchronous activation sequence. Finally, modifying the activation sequence by ventricular pacing substantially changed unipolar voltage amplitudes in patients and computer models.

Together these results strongly indicate that activation sequence is a major determinant of local unipolar voltage amplitude and that the low septal voltage amplitudes in LBBB hearts can be explained exclusively by the specific activation sequence.

The septum: a challenging myocardial region

In our data, endocardial EAM LBBB patients demonstrated smaller unipolar voltage amplitudes in the septum compared with other LV

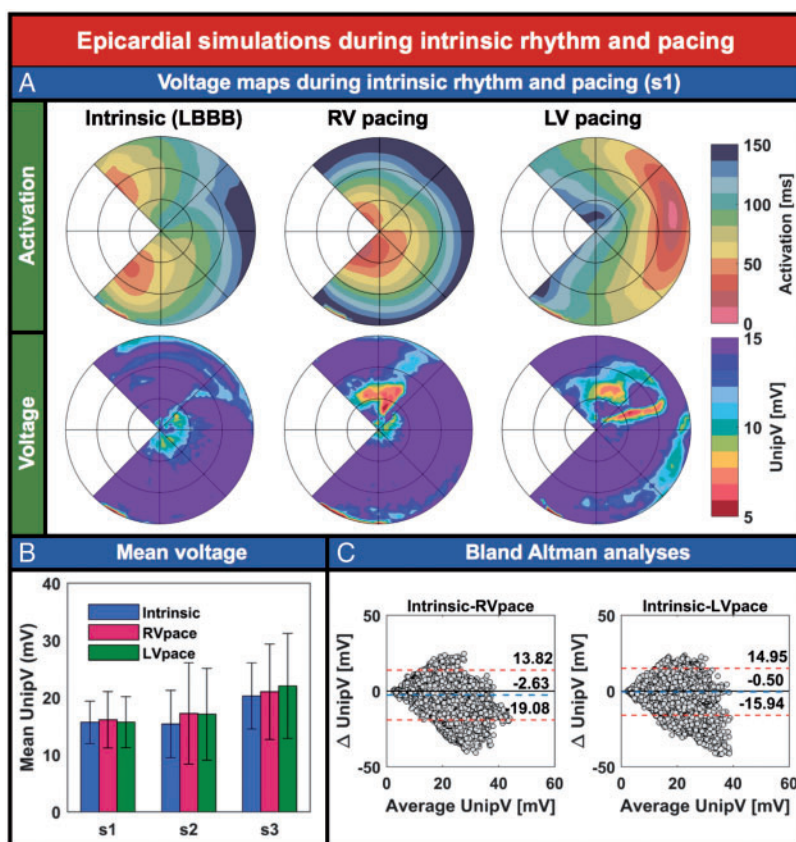


Figure 5 Pacing-induced unipolar voltage amplitude (UnipV) changes at the epicardium in computer models. (A) Epicardial UnipV maps of computer simulation s1 during different activation sequences induced by pacing. The septal quarters are displayed in white as the epicardium does not contain septum. (B) Mean UnipV for every computer model during different activation sequences. (C) Bland–Altman analyses comparing the difference between intrinsic (LBBB) and paced UnipVs. Similarly, like the clinical data, the mean UnipVs do not change much, but substantial point-by-point changes are observed. LBBB, left bundle branch block; LV, left ventricular; RV, right ventricular.

segments. This difference was substantial [average 4.5 mV (~33% lower)] and present in every single patient. More interesting, these regional unipolar voltage amplitude differences disappeared after restoring a normal activation sequence in the computer models, indicating that these low septal voltage amplitudes are exclusively due to an LBBB activation sequence, as geometrical and tissue properties were kept constant in the model. Low septal unipolar voltage amplitudes have not previously been associated with an LBBB activation sequence, although substantial regional variation in septal voltage amplitudes have been reported by Tung *et al.*⁸

Detailed EAM studies by Auricchio *et al.*⁹ showed that an LBBB activation sequence is characterized by a slow impulse conduction originating from the RV free wall gradually propagating to the LV lateral wall. Long transseptal times, typically >30 ms, were also demonstrated by endocardial mapping in LBBB patients¹⁸ and in canine LBBB hearts.¹⁹ A long transseptal time reflects an electrical separation between the RV and LV and slow transseptal conduction. The slow conduction across the septum during LBBB activation may be explained by an activation sequence propagating perpendicular to the fibre orientation. Propagation velocity perpendicular to the fibre

orientation is half of that along the fibre direction.²⁰ Interestingly, LBBB even in the absence of reduced LV function already causes regional changes in conduction velocity by lateralization of connexin43.²¹ Thus, low septal unipolar voltage amplitudes (in the absence of scar) during LBBB activation sequences may be partially explained by slow conduction across the septum.

Pacing-induced voltage changes

The substantial pacing-induced voltage amplitude changes in the LV free wall support the idea that activation sequence-created low-voltage amplitudes are not a specific property of the septum. Moreover, because during RV pacing there is a whole range of activation sequences within the LV free wall, also a wide range of changes (both increases and decreases) were observed. Clearly, these changes were substantial and more variable at the epicardium (mean absolute difference: 3.6–6.2 mV corresponding to 40–53% of intrinsic value; IQR differences: 53–63% of intrinsic value) compared with the endocardium (mean absolute difference: 3.3–3.8 mV corresponding to 28–30% of intrinsic value; IQR differences: 37–40% of intrinsic value).

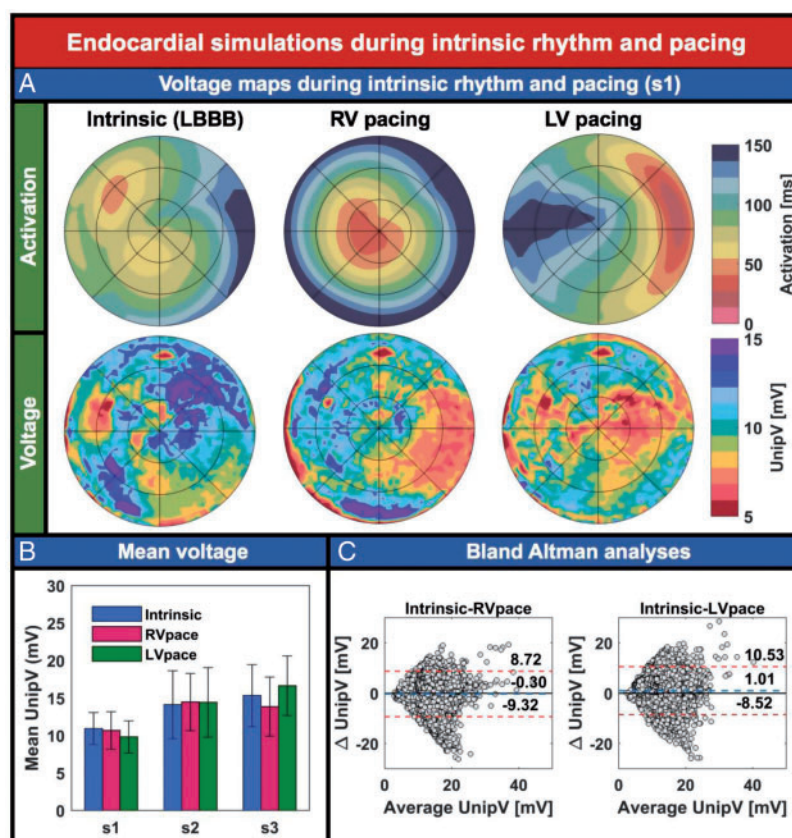


Figure 6 Pacing-induced unipolar voltage amplitude (UnipV) changes at the endocardium in computer models. (A) Endocardial UnipV maps of computer model s1 during different activation sequences induced by pacing. (B) Mean UnipV for every computer model during different activation sequences. (C) Bland–Altman analyses comparing the difference between intrinsic (LBBB) and paced UnipVs. LBBB, left bundle branch block; LV, left ventricular; RV, right ventricular.

Therefore, in using voltage maps for scar delineation, the activation sequence needs to be taken into account.⁸

The fact that we observe these wavefront dependencies of unipolar voltage amplitudes may be surprising, because they are considered to have a larger field of view compared to bipolar measurements. Several studies already investigated pacing-induced voltage changes, but these focused solely on bipolar measurements.^{22,23} Blauer et al.²³ confirmed in a bidomain model that different catheter inclination angles substantially impact the accuracy of identifying lesions by bipolar mapping. Brunckhorst et al.²² demonstrated in 11 ventricular tachycardia (VT) patients that RV pacing produced a >50% change in bipolar voltage at 28% sites and >100% at 10% sites. Therefore, it appears that, the range of fractional differences induced by the activation sequence is similar for unipolar and bipolar voltage measurements.

Pacing-induced changes in unipolar voltage amplitudes have been investigated in two studies to date. Tung et al.⁸ investigated the influence of changing wavefront on scar characterization (by low unipolar and bipolar recordings) in 29 VT patients. A variability of 22% for bipolar and 14% for unipolar voltage characterization of scar was observed with different activation sequences. Amorós-Figuera et al.²⁴

analysed voltage amplitude changes during intrinsic rhythm and RV pacing. In healthy myocardium, the IQR of change was 31% for endocardial unipolar voltage amplitudes, remarkably close to the IQR change of 37% that we observed after RV pacing in the computer models at the endocardium.

Clinical implications

To date, unipolar and bipolar voltage mapping are commonly used methods in clinical practice for invasive scar delineation.¹ In this study, we demonstrated that unipolar voltage amplitudes can be affected by different activation sequences and changes up to half of the intrinsic value are common. Furthermore, lower unipolar voltage amplitudes are present in the septum in patients with a LBBB activation sequence.

These findings advocate for additional methods of invasive scar delineation. One potential method would be integration of CMR imaging data into the EAM system.²⁵ Alternative novel approaches for more accurate invasive scar delineation include the use of impedance measurements²⁴ and the wavefront-independent omipolar electrograms.^{26,27}

Table 2 Computer model characteristics

Model	Fitted to patient	Conduction	Wavefronts	Mapping	Number of EGMs (endo/epi)
s1	p1	LBBB/normal	Intrinsic/RV/LV	LV endo/epi	4105/4540
s2	p2	LBBB/normal	Intrinsic/RV/LV	LV endo/epi	6732/6810
s3	p3	LBBB/normal	Intrinsic/RV/LV	LV endo/epi	5626/6574

EGMs, electrograms; LBBB, left bundle branch block; LV, left ventricle; RV, right ventricle.

Limitations

The study included both endocardially and epicardially mapped patients, which possibly affected voltage amplitudes. As such, this study focusses on relative voltage differences rather than absolute values. Moreover, we connected the two patient populations by using computer simulations from which we could extract both endocardial and epicardial data, covering the entire spectrum of patient data.

The present study primarily investigates unipolar voltage amplitudes, and therefore, additional studies are necessary to investigate the influence of activation sequence on bipolar voltage amplitudes.

Conclusion

This study demonstrates that an LBBB activation sequence in patients is associated with approximately 33% lower unipolar voltage amplitudes in the septum, and that these regional voltage amplitude differences resolve once a normal activation sequence is restored in a computer simulation. We additionally demonstrated that pacing-induced changes in the activation sequence substantially affect unipolar voltage amplitudes by approximately 30–50% of intrinsic value, particularly at the epicardium, while the direction of change can be both positive and negative. These findings are relevant for interpretation of voltage maps.

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References

- Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Europace* 2015;**17**:1601–87.
- Hutchinson MD, Gerstenfeld EP, Desjardins B, Bala R, Riley MP, Garcia FC et al. Endocardial unipolar voltage mapping to detect epicardial ventricular tachycardia substrate in patients with nonischemic left ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol* 2011;**4**:49–55.
- Nguyen UC, Maffessanti F, Mafi-Rad M, Conte G, Zeemering S, Regoli F et al. Evaluation of the use of unipolar voltage amplitudes for detection of myocardial scar assessed by cardiac magnetic resonance imaging in heart failure patients. *PLoS One* 2017;**12**:e0180637.
- Codreanu A, Odille F, Aliot E, Marie PY, Magnin-Poull I, Andronache M et al. Electroanatomic characterization of post-infarct scars comparison with 3-dimensional myocardial scar reconstruction based on magnetic resonance imaging. *J Am Coll Cardiol* 2008;**52**:839–42.
- Wijnmaalen AP, van der Geest RJ, van Huls van Taxis CF, Siebelink HM, Kroft LJ, Bax JJ et al. Head-to-head comparison of contrast-enhanced magnetic resonance imaging and electroanatomical voltage mapping to assess post-infarct scar characteristics in patients with ventricular tachycardias: real-time image integration and reversed registration. *Eur Heart J* 2011;**32**:104–14.
- Glashan CA, Androulakis AFA, Tao Q, Glashan RN, Wisse LJ, Ebert M et al. Whole human heart histology to validate electroanatomical voltage mapping in patients with non-ischaemic cardiomyopathy and ventricular tachycardia. *Eur Heart J* 2018;**39**:2867–75.
- Josephson ME, Anter E. Substrate mapping for ventricular tachycardia: assumptions and misconceptions. *JACC Clin Electrophysiol* 2015;**1**:341–52.
- Tung R, Josephson ME, Bradfield JS, Shivkumar K. Directional influences of ventricular activation on myocardial scar characterization: voltage mapping with multiple wavefronts during ventricular tachycardia ablation. *Circ Arrhythm Electrophysiol* 2016;**9**:pii:e004155.
- Auricchio A, Fantoni C, Regoli F, Carbucicchio C, Goette A, Geller C et al. Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. *Circulation* 2004;**109**:1133–9.
- Mafi Rad M, Blaauw Y, Dinh T, Pison L, Crijns HJ, Prinzen FW et al. Different regions of latest electrical activation during left bundle-branch block and right ventricular pacing in cardiac resynchronization therapy patients determined by coronary venous electro-anatomic mapping. *Eur J Heart Fail* 2014;**16**:1214–22.
- Potse M, Krause D, Kroon W, Murzilli R, Muzzarelli S, Regoli F et al. Patient-specific modelling of cardiac electrophysiology in heart-failure patients. *Europace* 2014;**16**:iv56–61.
- Nguyen UC, Potse M, Regoli F, Caputo ML, Conte G, Murzilli R et al. An in-silico analysis of the effect of heart position and orientation on the ECG morphology and vectorcardiogram parameters in patients with heart failure and intraventricular conduction defects. *J Electrocardiol* 2015;**48**:617–25.
- Krause D, Potse M, Dickopf T, Krause R, Auricchio A, Prinzen FW. Hybrid parallelization of a large-scale heart model. In: Keller R, Kramer D, Weiss J-P (eds).

- Facing the Multicore-Challenge II*. Lecture Notes in Computer Science; Aspects of New Paradigms and Technologies in Parallel Computing. Vol. 7174. Berlin: Springer; 2012. p120–32.
14. Potse M, Dubé B, Richer J, Vinet A, Gulrajani RM. A comparison of monodomain and bidomain reaction-diffusion models for action potential propagation in the human heart. *IEEE Trans Biomed Eng* 2006;**53**:2425–35.
 15. ten Tusscher KH, Noble D, Noble PJ, Panfilov AV. A model for human ventricular tissue. *Am J Physiol Heart Circ Physiol* 2004;**286**:H1573–89.
 16. Potse M, Dubé B, Vinet A. Cardiac anisotropy in boundary-element models for the electrocardiogram. *Med Biol Eng Comput* 2009;**47**:719–29.
 17. White J, Rassweiler A, Samhoury J, Stier A, White C. Ecologists should not use statistical significance tests to interpret simulation model results. *Oikos* 2014;**123**: 385–8.
 18. Prinzen FW, Auricchio A. Is echocardiographic assessment of dyssynchrony useful to select candidates for cardiac resynchronization therapy? Echocardiography is not useful before cardiac resynchronization therapy if QRS duration is available. *Circ Cardiovasc Imaging* 2008;**1**:70–7; discussion 8.
 19. Strik M, van Deursen CJ, van Middendorp LB, van Hunnik A, Kuiper M, Auricchio A et al. Transseptal conduction as an important determinant for cardiac resynchronization therapy, as revealed by extensive electrical mapping in the dyssynchronous canine heart. *Circ Arrhythm Electrophysiol* 2013;**6**: 682–9.
 20. Spach MS, Miller WT 3rd, Geselowitz DB, Barr RC, Kootsey JM, Johnson EA. The discontinuous nature of propagation in normal canine cardiac muscle. Evidence for recurrent discontinuities of intracellular resistance that affect the membrane currents. *Circ Res* 1981;**48**:39–54.
 21. Spragg DD, Akar FG, Helm RH, Tunin RS, Tomaselli GF, Kass DA. Abnormal conduction and repolarization in late-activated myocardium of dyssynchronously contracting hearts. *Cardiovasc Res* 2005;**67**:77–86.
 22. Brunckhorst CB, Delacretaz E, Soejima K, Maisel WH, Friedman PL, Stevenson WG. Impact of changing activation sequence on bipolar electrogram amplitude for voltage mapping of left ventricular infarcts causing ventricular tachycardia. *J Interv Card Electrophysiol* 2005;**12**:137–41.
 23. Blauer JJ, Swenson D, Higuchi K, Plank G, Ranjan R, Marrouche N et al. Sensitivity and specificity of substrate mapping: an in silico framework for the evaluation of electroanatomical substrate mapping strategies. *J Cardiovasc Electrophysiol* 2014;**25**:774–80.
 24. Amorós-Figueras G, Jorge E, Alonso-Martin C, Traver D, Ballesta M, Bragos R et al. Endocardial infarct scar recognition by myocardial electrical impedance is not influenced by changes in cardiac activation sequence. *Heart Rhythm* 2017;**15**: 589–96.
 25. Nguyen UC, Mafi-Rad M, Aben JP, Smulders MW, Engels EB, van Stipdonk AM et al. A novel approach for left ventricular lead placement in cardiac resynchronization therapy: intraprocedural integration of coronary venous electroanatomic mapping with delayed enhancement cardiac magnetic resonance imaging. *Heart Rhythm* 2017;**14**:110–9.
 26. Deno DC, Balachandran R, Morgan D, Ahmad F, Masse S, Nanthakumar K. Orientation-independent catheter-based characterization of myocardial activation. *IEEE Trans Biomed Eng* 2017;**64**:1067–77.
 27. Masse S, Magtibay K, Jackson N, Asta J, Kusha M, Zhang B et al. Resolving myocardial activation with novel omnipolar electrograms. *Circ Arrhythm Electrophysiol* 2016;**9**:e004107.